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Full Length Article

Residual anticoagulation activity in atrial fibrillation patients with temporary interrupted direct oral anticoagulants: Comparisons across 4 drugs

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ABSTRACT

Background: Atrial fibrillation (AF) ablation with minimally interrupted direct oral anticoagulants (DOACs) predominates, possibly raising concern about their remaining activity during the procedure. We aimed to examine residual activities of 4 different DOACs.

Methods: The serum DOAC concentration and anti-factor Xa activity were measured 3 and 24 h after the last intake in patients undergoing AF ablation who were treated with rivaroxaban, apixaban, edoxaban, or dabigatran.

Results: The reduction in the apixaban concentration between the 2 blood sampling time points (N = 32, mean ± SD, −67.7 ± 14.8% [231.6 ± 93.1 to 71.9 ± 31.8 ng/mL]) was smaller than that for rivaroxaban (N = 28, −83.6 ± 10.9% [234.2 ± 96.6 to 34.3 ± 19.8 ng/mL]; P < 0.001) and dabigatran (N = 20, −90.7 ± 7.3% [135.3 ± 68.3 to 12.6 ± 10.6 ng/mL]; P < 0.001), with its greatest value measured 24 h after the last intake in the apixaban group. The decrease in the anti-factor Xa activity was also smaller in the patients with apixaban (−73.8 ± 12.7%) than with rivaroxaban (−87.9 ± 7.9%; P < 0.001) and edoxaban (N = 22, −81.9 ± 15.2%; P = 0.049), and its remaining activity 24 h after the last dose was the highest in the apixaban group. A serum DOAC concentration measured 24 h after the last dose of > 30 ng/mL was seen in 41 (51.3%) patients with rivaroxaban, apixaban, or dabigatran, and it was independently associated with apixaban versus rivaroxaban (odds ratio 5.0; P = 0.01) and apixaban versus dabigatran (odds ratio 74.0; P < 0.001).

Conclusion: The pattern of drug elimination from blood may vary depending on DOACs, and their residual activity may not be negligible even 24 h after the last intake.

1. Introduction

Anticoagulation with direct oral anticoagulants (DOACs) is a cornerstone of stroke prevention throughout the periprocedural period of atrial fibrillation (AF) ablation. According to the landmark trials [1–4], it is difficult to decide which is the best among the 4 currently available DOACs. However, it is still important to understand the pharmacodynamic characteristics of each DOAC in order to tailor the anticoagulation treatment to an individual patient. AF ablation strategies with briefly interrupted or even uninterrupted DOACs are currently mainstream [5–7]. That may raise the following question, “Are the residual effects of DOACs small enough to be neglected during the ablation procedure when they are temporally withheld?”. The goal of the present study was to compare the remaining activities of the 4 different DOACs and their potential clinical significance during the periprocedural period of AF ablation.

2. Methods

The present study was conducted at Hiroshima University Hospital from April 2017 to March 2018. The study protocol was approved by the research committee of the institution. Consecutive patients with drug-refractory AF were considered eligible for inclusion if they were scheduled to undergo radiofrequency catheter ablation for the first time and had been anticoagulated for at least 4 weeks with the use of a standard dose of DOACs including rivaroxaban, apixaban, edoxaban,

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and dabigatran. Patients were excluded if they were being prescribed with antiplatelet drugs, verapamil, or amiodarone. Prior to the ablation, all the participants were checked for left atrial thrombi with the use of transesophageal echocardiography. The eligible patients were enrolled after giving informed consent.

2.1. Oral anticoagulation regimens

Eligible patients had been prescribed one of the following 4 DOACs for at least 4 weeks before the ablation: rivaroxaban, apixaban, edoxaban, and dabigatran. The choice of the DOAC was left to the discretion of each referring physician. On the basis of the current guidelines on the use of DOACs [8] or landmark trials [1,3,4], the standard doses of apixaban, edoxaban, and dabigatran were determined as 5 mg BID, 60 mg OD, and 150 mg BID, respectively. Although the guidelines [8] recommend a 20 mg OD as a standard dose for rivaroxaban, we in the present study determined to adopt its Japan-specific standard dose of 15 mg OD, based on the J-ROCKET AF trial [9] that included only Japanese patients. Patients with a reduced dose of DOACs were not included. Patients with OD or BID dosing regimens were instructed to take the total dose or morning dose, respectively, between 7:30 and 8:30 AM. Patients with BID dosing regimens were encouraged to take the evening dose between 7:30 and 8:30 PM. According to the guidelines [8], the timing of the last intake was determined as 24 h before the ablation procedure for all 4 DOACs regardless of whether they had QD or BID dosing regimens. Once the ablation was over, each DOAC was resumed with a normal dose regimen (Table 1). A bridging therapy with heparin was not applied.

2.2. Measurements of the anti-factor Xa activity and DOAC concentration

Blood samples were collected on two separate occasions in each patient. The first one was obtained 3 h after the last DOAC intake to measure its peak serum level, and the second one was taken 24 h after the last oral administration to check for any residual anticoagulant activity (Table 1). The samples were centrifuged within 1 h after the sampling, and then were stored frozen at −80 °C until analyzed. Chromogenic anti-factor Xa assays were performed to measure the anti-factor Xa activity of rivaroxaban, apixaban, and edoxaban, with the use of HemosIL® Liquid Heparin (Instrumentation Laboratory, Bedford, MA, USA). Dedicated calibrators and controls were used to determine the concentrations of rivaroxaban and apixaban. Edoxaban's concentration was not measured because no edoxaban specific calibrators were commercially available during the study period. The concentration of dabigatran was measured with the use of the diluted thrombin time (HemosIL® Direct Thrombin Inhibitor; Instrumentation Laboratory) and specific controls and calibrators. There is a consensus that DOACs can exert their anticoagulation action to a certain extent as long as their serum concentration is > 30 ng/mL even though it is below the trough level [8,10,11]. Therefore, if the serum DOAC concentration measured 24 h after the last intake was > 30 ng/mL, it was considered a clinically significant residual concentration in patients with rivaroxaban, apixaban, and dabigatran. All assays were performed on a commercially available analyzer (ACL-TOP® 300 CTS; Instrumentation Laboratory).

2.3. Anticoagulation during ablation

An initial heparin bolus of 100 units/kg was intravenously administered immediately following the sheath insertion. An additional heparin bolus of 20–60 units/kg was given to achieve a clotting time of 300–350 s, if necessary. The activated clotting time was checked with the use of a dedicated analyzer (Hemochron® Response, International Technidyne Corporation, Edison, NJ, USA) at 10-minute intervals until its target value was achieved, and then at 30 minute intervals for the duration of the procedure. A 20 mg dose of protamine was infused to reverse the heparin at the end of the procedure.

2.4. Ablation procedure

The details of the double Lasso catheter-guided extensive encircling pulmonary vein antrum isolation performed in this study have been described previously [12]. In brief, 2 decapolar circular catheters were positioned within the ipsilateral superior and inferior pulmonary veins. Circumferential ablation lines were created around the left- and right-sided ipsilateral pulmonary veins with the use of a 3.5-mm-tip irrigated catheter (Thermocool SmartTouch®, Biosense Webster, Diamond Bar, CA, USA). Radiofrequency energy was delivered with a maximum power of 30 W. Real-time contact force data were used to guide the ablation procedures, with a target force of 10–15 g. The goal of the procedure was to achieve both pulmonary vein entrance and exit block. The ablation procedures were performed in the morning.

2.5. Endpoints

The endpoints were the (1) serum DOAC concentration and anti-factor Xa activity before and after its transient withdrawal and (2) thromboembolic or bleeding events occurring during the periprocedural period.

2.6. Statistical analysis

The continuous variables are summarized as the means ± SD or means ± SE, and categorical variables as proportions. The differences in the categorical variables across the groups were examined with the use of a Pearson Chi-Square test or Fisher's exact test. A one-way analysis of variance was used to compare the normally distributed variables across the groups, and it was followed by a post hoc pairwise comparison with Tukey–Kramer test as appropriate. Comparisons of the paired data were done by means of a Wilcoxon signed-rank test. Univariate and multivariate logistic regression models were used to determine the factors independently associated with the serum DOAC concentration measured 24 h after the last dose of > 30 ng/mL. Likely parameters were included as explanatory variables in the models. Variables with statistical significance in the univariate analyses were further included in the multivariate models. All statistical analyses were performed with the use of JMP software version 13.0 (SAS Institute, Cary, NC, USA). A P value of < 0.05 was considered significant.

Table 1
Dosing regimens and blood sampling schedule.

	Day −2		Day −1		Day of operation		Day +1	
	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
Rivaroxaban, edoxaban intake	●		●				●	
Apixaban, dabigatran intake	●	●	●			●	●	●
Blood sampling			●[a]		●[b]			

[a] 3 h after the last intake.
[b] 24 h after the last intake.

Table 2
Baseline characteristics of the study population.

Variables	Rivaroxaban	Apixaban	Edoxaban	Dabigatran	P value
	N = 28	N = 32	N = 22	N = 20	
Age (years)	63 ± 10	67 ± 10	61 ± 8	58 ± 8*	0.01
Male	24 (85.7%)	19 (59.4%)	19 (86.4%)	16 (80%)	0.05
Weight (kg)	69.5 ± 11.1	65.8 ± 14.6	73.6 ± 12.6	73.7 ± 14.9	0.1
Atrial fibrillation type					0.13
Paroxysmal	23 (82.1%)	23 (71.9%)	12 (54.6%)	10 (50%)	
Persistent	3 (10.7%)	8 (25%)	6 (27.3%)	6 (30%)	
Longstanding persistent	2 (7.1%)	1 (3.1%)	4 (18.2%)	4 (20%)	
CHA_2DS_2-VASc score					0.006
0–1	10 (35.7%)	5 (15.6%)	13 (59.9%)	12 (60%)	
2	9 (32.1%)	10 (31.2%)	6 (27.3%)	5 (25%)	
3–10	9 (32.1%)	17 (53.1%)	3 (13.6%)	3 (15%)	
Previous stroke or TIA	1 (3.6%)	4 (12.5%)	0	3 (15%)	0.18
Heart failure	2 (7.1%)	5 (15.6%)	4 (18.2%)	2 (10%)	0.63
Hypertension	20 (71.4%)	23 (71.9%)	12 (54.6%)	12 (60%)	0.48
Diabetes	7 (25%)	8 (25%)	2 (9.1%)	2 (10%)	0.27
Left ventricular ejection fraction (%)	62.3 ± 4.3	59.6 ± 7.3	58.3 ± 8.2	56.2 ± 8.6†	0.03
Left atrial volume index (mL/m^2)	42 ± 16	41 ± 14	42 ± 11	37 ± 8	0.5
Serum creatinine (mg/dL)	0.87 ± 0.16	0.81 ± 0.16	0.82 ± 0.16	0.83 ± 0.16	0.48
eGFR (ml/min/1.73 m^2)	68.5 ± 13.3	67.8 ± 12.5	73.7 ± 15.1	72.7 ± 15	0.33

Data are presented as the n (%), or mean ± SD. The CHA2DS2-VASc score is a measure of the risk of a stroke in which congestive heart failure, hypertension, an age of 65–74 years, diabetes mellitus, vascular disease, and a female sex are each assigned 1 point, and an age of 75 years or older and a previous stroke or transient ischemic attack are each assigned 2 points; the score is calculated by summing all the points in each patient. TIA = transient ischemic attack, eGFR = estimate glomerular filtration rate.

* P = 0.001 vs. apixaban.

† P = 0.02 vs. rivaroxaban.

3. Results

3.1. Patients

A total of 106 patients matched the inclusion criteria. Among them, 4 patients were excluded due to the concomitant use of aspirin or amiodarone. We thus finally studied 102 patients: 28 with rivaroxaban, 32 with apixaban, 22 with edoxaban, and 20 with dabigatran. The baseline clinical characteristics are presented in Table 2.

3.2. Anti-factor-Xa activity and the DOAC concentration

The anti-factor-Xa activity 3 h after the last intake significantly differed across the patients treated with rivaroxaban, apixaban, and edoxaban (mean ± SD, 1.98 ± 0.86, 1.59 ± 0.71, and 1.17 ± 0.38 IU/mL; P < 0.001), with the highest level in patients with rivaroxaban. The anti-factor-Xa activity decreased dramatically 24 h after the last dose in each patient group (all P < 0.001), and at that moment, the patients with apixaban in turn had a higher level than either those with rivaroxaban or edoxaban (mean ± SD, 0.39 ± 0.23 vs. 0.2 ± 0.12 and 0.2 ± 0.17 IU/mL; P < 0.001 for each, Fig. 1A). Patients with apixaban presented with a significantly smaller reduction in the anti-factor-Xa activity than the patients with rivaroxaban or edoxaban (mean ± SD, −73.8 ± 12.7 vs. −87.9 ± 7.9 and −81.9 ± 15.2%; P < 0.001 and P = 0.049, respectively, Fig. 1B). The serum drug concentration measured 3 h after the last intake was significantly lower in the patients with dabigatran than in those with rivaroxaban (P < 0.001) or apixaban (P < 0.001, Fig. 2A). Although the serum concentration of rivaroxaban, apixaban, and dabigatran decreased greatly during the 21 h between the 2 blood sampling time points (mean ± SD, 234.2 ± 96.6 to 34.3 ± 19.8, 231.6 ± 93.1 to 71.9 ± 31.8, and 135.3 ± 68.3 to 12.6 ± 10.6 ng/mL; P < 0.001 for each), the reduction rate in the apixaban concentration was markedly smaller compared to that of both rivaroxaban and dabigatran (mean ± SD, −67.7 ± 14.8 vs. −83.6 ± 10.9 and −90.7 ± 7.3%; P < 0.001 for each, Fig. 2A and B), and consequently, the apixaban concentration was the highest at the 2nd blood samplings. We found a serum DOAC concentration of > 30 ng/mL measured 24 h after the last intake in 41 (51.3%) patients with rivaroxaban, apixaban, or dabigatran, and it was more common in those given apixaban than in those given rivaroxaban or dabigatran (84.4% vs. 46.4% and 5%; P < 0.001). Apixaban vs. rivaroxaban (P = 0.01), rivaroxaban vs. dabigatran (P = 0.009), and apixaban vs. dabigatran (P < 0.001) were found to be independently associated with the serum drug concentration of > 30 ng/mL 24 h after the last dose in the multiple logistic regression models including an older age, female sex, smaller body surface area, reduced renal function, and DOACs used (Table 3). The total heparin requirement during the ablation procedure was similar across the 4 patient groups (rivaroxaban, apixaban, edoxaban, and dabigatran; mean ± SD, 11214.3 ± 2891.3, 10,475 ± 3096.9, 11,166.7 ± 3805.7, and 12,275 ± 3581.7 U; P = 0.31).

3.3. Safety outcomes

The planned ablation procedures were carried out successfully in all patients included. No serious complications were noted, including thromboembolic events, cardiac tamponade, esophageal injury, or massive bleeding. The procedural duration was similar across the 4 patient groups (rivaroxaban, apixaban, edoxaban, and dabigatran; mean ± SD, 4.3 ± 1.2, 3.9 ± 0.9, 4.0 ± 1, and 4.0 ± 0.8 h; P = 0.65).

4. Discussion

4.1. Major findings

The major findings in the present study were threefold: (i) the reduction in the anti-factor-Xa activity and serum drug concentration following the transient withdrawal was smaller, and the remaining effect measured 24 after the last intake was higher in the patients with apixaban than in those with rivaroxaban, edoxaban, and dabigatran, (ii) a clinically significant anticoagulation action remained even 24 h after the last dose in the majority of the patients, and (iii) no thromboembolic or bleeding complications were noted during the peri-ablation period.

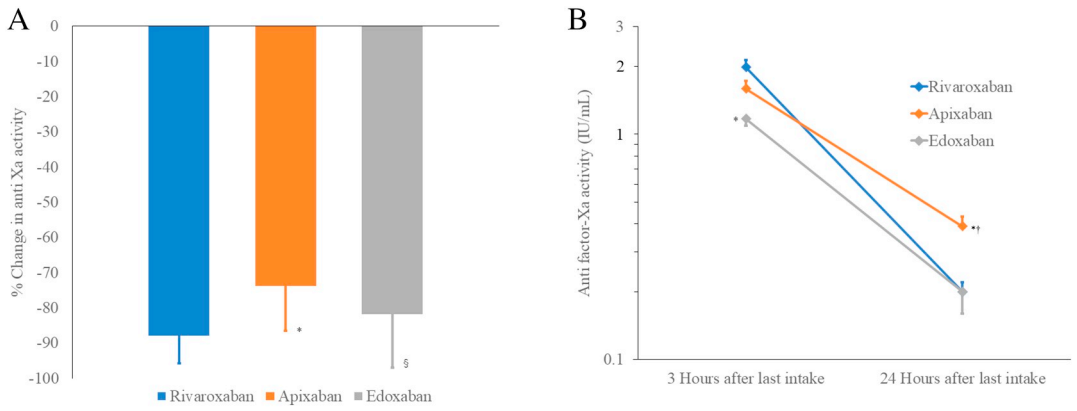

Fig. 1. The change in the actual measured value of the anti-factor-Xa activity 3 and 24 h after the last intake of direct oral anticoagulants (DOACs, A), and the percent change (B) according to the 3 different DOACs. The means and standard errors are presented. *P < 0.001, versus rivaroxaban †P < 0.001, versus edoxaban, §P = 0.049, versus apixaban.

4.2. Potential prolonged action of apixaban following its withdrawal

The 4 DOACs have comparable half-lives and time to the maximum plasma concentration to each other [8,13]. It is therefore theoretically possible that their residual effects long after the half-lives do not differ much when they are temporally interrupted. The first major finding of the present study, however, indicated that this theoretical speculation was not the case in the real clinical practice setting. Two studies [14,15] examined the residual serum concentrations of the different DOACs measured during their perioperative interruption. None of them reported any clear pharmacodynamic characteristics of apixaban that possibly would prolong its residual action. Would our findings be "heretical"? One of the 2 studies [15], however, showed that the serum concentration of apixaban measured ≥48 h after the last dose was ≥50 ng/mL in 5 out of 18 patients with apixaban while none of 23 patients with rivaroxaban had its concentration exceeding 50 ng/mL. To date, only a limited number of studies are available regarding bleeding complications that occur following elective surgeries in patients with skipped doses of DOACs. Among them, a study on open heart surgery [16] reported tendencies toward a higher occurrence of a re-thoracotomy due to postoperative bleeding and a longer stay in the intensive care unit in patients with skipped doses of apixaban compared to those with interrupted rivaroxaban and dabigatran. Those two studies may suggest that apixaban needs more time than the other DOACs to eliminate the residual action after its discontinuation, and thus supports our first major finding.

4.3. Is the residual DOAC activity negligibly small?

In the present study, all DOACs were withdrawn on the basis of the recommendation of the current guidelines [8]. Nevertheless, over half of the patients kept a serum DOAC level with a clinically significant anticoagulation action (> 30 ng/mL) even 24 h after the last intake. Similar findings were reported in the previous studies [14,15]. Therefore, although we did not encounter any bleeding events, it may be controversial whether or not the residual DOAC activity 24 h after the last dose can be ignored.

4.4. Limitations

We did not measure edoxaban's concentration owing to a lack of any commercially available edoxaban specific calibrators. The present study was not a randomized one, and therefore a significant bias was included. Finally, the present study did not include patients large enough in number to compare the safety outcomes, which also limited the statistical power of the analyses.

4.5. Clinical implications

The present study is among the few studies that have compared the residual effects of the 4 DOACs [14,15]. Our findings suggest that their anticoagulation action may not be negligible even 24 h after the last intake, and the patterns of the drug elimination from the blood may vary depending on the DOAC. Therefore, from the viewpoint of the

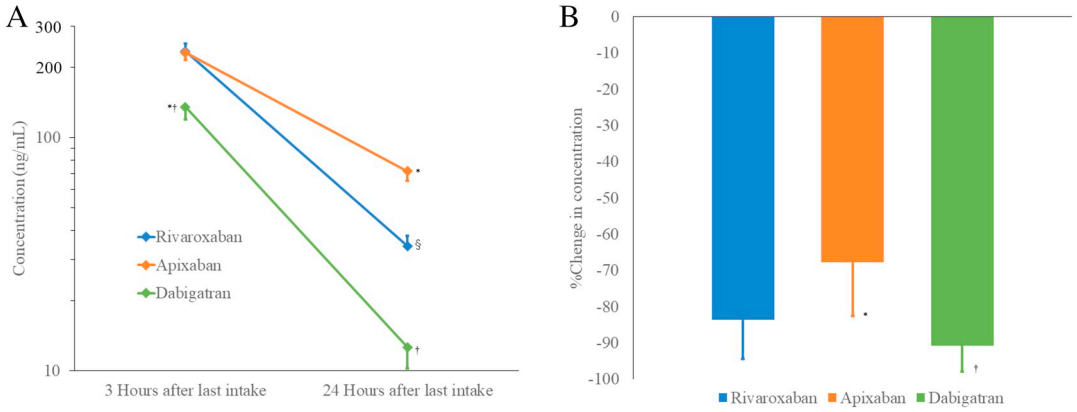

Fig. 2. The change in the actual measured value of the serum DOAC concentration 3 and 24 h after the last intake, and the percent change (B) according to the 3 different DOACs. The means and standard errors are presented. *P < 0.001, versus rivaroxaban, †P < 0.001, versus apixaban, §P = 0.02, versus dabigatran.

Table 3
Odds ratio for a DOAC concentration of > 30 ng/mL 24 h after the last dose (N = 80).

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age ≥ 65 years	7.9 (2.9–21.4)	< 0.001	3.0 (0.8–11.5)	0.1
Female	4.4 (1.5–14.8)	0.007	3.7 (0.6–30.5)	0.15
Body surface area < 1.73 m2	3.3 (1.3–8.5)	0.01	1.4 (0.3–6.5)	0.63
eGFR < 60 ml/min/1.73 m^2	1.4 (0.5–3.9)	0.53		
Apixaban vs. rivaroxaban	6.2 (1.9–20.9)	0.003	5.0 (1.4–20.2)	0.01
Rivaroxaban vs. dabigatran	16.5 (2.8–316.3)	< 0.001	14.7 (1.8–343.8)	0.009
Apixaban vs. dabigatran	102.6 (11.1–950.2)	< 0.001	74.0 (9.3–1758.1)	< 0.001

DOAC = direct oral anticoagulant, CI = confidence interval, eGFR = estimated glomerular filtration rate.

choice of the DOAC, the present study may provide new insight into the field of anticoagulation therapy.

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Declaration of competing interest

None declared.

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